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| 10/027,807 | 10/19/2001 | Li Gan | 019488-000711US | 9177 |

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BOZICEVIC, FIELD & FRANCIS LLP
200 MIDDLEFIELD RD
SUITE 200
MENLO PARK, CA 94025

| EXAMINER |
|---|
| CHAKRABARTI, ARUN K |

| ART UNIT | PAPER NUMBER |
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| 1634 | |

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Please find below and/or attached an Office communication concerning this application or proceeding.

# Office Action Summary

| Application No. | Applicant(s) |
|---|---|
| 10/027,807 | Gan |
| **Examiner** | **Art Unit** |
| Arun Chakrabarti | 1634 |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1) ☒ Responsive to communication(s) filed on *Mar 19, 2003* .

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

**Disposition of Claims**

4) ☒ Claim(s) *14, 15, 17, 19, 20, 22-25, 27, 29-31, 34-36, 43, 45-47, and 51-55* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *14, 15, 17, 19, 20, 22-25, 27, 29-31, 34-36, 43, 45-47, and 51-55* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

**Application Papers**

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Detailed Action*

## DETAILED ACTION

### *Specification*

1. Claims 1-13,16, 18, 21, 26, 28, 32-33, 37-42, 44 and 48-50 are canceled. Claims 14-15, 17, 19-20, 23-25, 27, 29, 30, 34-36, 43, 45, 46, and 51 have been amended. New claims 52-55 have been added.

### *Claim Rejections - 35 USC § 103*

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CAR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was

made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 14-15, 17, 23-25, 30, 31, 34-36, 43, and 52-53 are rejected under 35 U.S.C. 103(a) over Leptin (U.S. Patent 6,135,942) (October 24, 2000) in view of Der et al (U.S. Patent 6,077,686) (June 20, 2000).

Leptin teaches a method for producing and identifying an active double stranded RNA (dsRNA) which attenuates a desired gene expression in a cell (Abstract), the method comprising:

a) producing a plurality of cDNA, wherein each cDNA comprises at least a portion of a gene that is expressed in a cell (Example);

b) producing a candidate dsRNA from at least one of the cDNA (Figures 4A and 4B and Column 43, lines 25-35);

c) introducing the candidate dsRNA into a reference cell (Column 43, lines 41-43); and

d) identifying an active dsRNA by determining whether the candidate dsRNA modulates a desired candidate gene expression in the reference cell (Column 43, lines 43-45 ).

Leptin teaches a method, wherein the step of identifying the active dsRNA comprises:

a) selecting a candidate gene, wherein the candidate gene is a gene that is expressed in a test cell and/or a control cell, and/or is expressed at a detectably different level with respect to the test cell and the control cell, and the test cell and the control cell differ with respect to a cellular characteristic ( Column 43, line 46 to Column 44, line 34); and

b) identifying whether the candidate dsRNA is an active dsRNA by determining whether down-regulation of expression of the candidate gene in a reference cell has a functional effect in the reference cell, wherein the determining comprises:

I) introducing the candidate dsRNA which is substantially identical to at least a part of the candidate gene into the reference cell (Column 43, lines 41 to Column 44, line 7); and

ii) detecting an alteration in a cellular activity or a cellular state in the reference cell, alteration indicating that the candidate gene plays a functional role in the reference cell and is an active dsRNA (Column 43, lines 43-45 ).

Leptin teaches a method, wherein the step of producing a plurality of cDNA comprises:

I) isolating at least one mRNA from the cell (Example and Column 43, lines 59-61 ), and

ii) producing a double-stranded cDNA from the isolated mRNA by reverse transcription (Example).

Leptin teaches a method for identifying and validating the effect of an active dsRNA which attenuates a desired gene expression in a cell (Example and Claims 8-9 and Column 46, line 6 to Column 47, line 46 ) and also a method for correlating genes and gene function, the method comprising:

a) producing a candidate dsRNA which comprises at least a portion of a candidate gene that is expressed in a control cell (Column 43, lines 41 to Column 44, line 7);

b) introducing the candidate dsRNA into a reference cell (Column 43, lines 41 to Column 44, line 7); and

c) identifying whether the candidate dsRNA is an active dsRNA by detecting an alteration in a cellular activity or a cellular state in the reference cell, alteration indicating that the candidate gene plays a functional role in the reference cell and is an active dsRNA (Example).

Leptin teaches a method, wherein the plurality of cDNA is produced from a plurality of mRNAs which are produced by the control cell (Example).

Leptin teaches a method, wherein the step of producing the plurality of candidate dsRNA comprises:

a) selecting a candidate gene, wherein the candidate gene is a gene that is expressed in a test cell and/or a control cell, and/or is expressed at a detectably different level with respect to the test cell and the control cell, and the test cell and the control cell differ with respect to a cellular characteristic (Example); and

b) producing the plurality of candidate dsRNAs, wherein each candidate dsRNA is substantially identical to at least a part of the candidate gene (Example).

Leptin teaches a method, wherein the candidate gene is selected from a normalized library prepared from cells of the same type as the test cell or the control cell and is present in low abundance in the normalized library. (Example)

Leptin teaches a method, wherein the candidate gene is a differentially expressed gene selected from a subtracted library that is enriched for genes that are differentially expressed with respect to the test cell and the control cell (Column 43, line 13 to Column 44, line 34).

Leptin teaches a method, wherein the subtracted library is also normalized and the candidate gene is one of the genes that is both present in low abundance and differentially expressed in the subtracted and normalized library (Example).

Leptin teaches a method, wherein the cellular characteristic is cell health, the test cell is diseased cell and the control cell is a healthy cell, and the candidate gene is potentially correlated with a disease (Column 41, line 33 to Column 44, line 34 and Example).

Leptin teaches a method, wherein the cellular characteristic is stage of development and the test cell and the control cell are at different stages of development, and the candidate gene is potentially correlated with mediating the change between the different stages of development (Example and Column 48, lines 56-62).

Leptin teaches a method, wherein the cellular characteristic is cellular differentiation and the candidate gene is potentially correlated with controlling cellular differentiation (Column 47, line 56 to Column 48, line 11).

Leptin teaches a method, wherein the candidate gene is an endogenous gene of the reference cell (Column 66, line 20 to Column 67, line 58).

Leptin teaches a method, wherein the candidate gene is present in the reference cell as an extrachromosomal gene (Example).

Leptin teaches a method, wherein the reference cell is part of a tissue of an organism (Column 48, lines 12-62)

Leptin teaches a method, wherein the reference cell is a mammalian cell (Column 35, lines 4-32).

Leptin teaches a method, wherein the reference cell is part of an organism and the detecting step comprises detecting a change in phenotype (Column 47, line 56 to Column 48, line 11).

Leptin teaches a method, wherein the determining step comprises determining whether interference with expression of the candidate gene in the reference cell is correlated with alteration of acellular activity or cellular state (Column 47, line 56 to Column 48, line 11).

Leptin teaches a method, wherein interference is achieved by introducing a double-stranded RNA into the reference cell that can specifically hybridize to the candidate gene (Example and Column 43, line 66 to Column 44, line 7).

Leptin does not teach the method wherein the test cell is obtained from a mammal that has had a stroke or neurological disease.

Der et al teaches the method wherein the test cell is obtained from a mammal that has had a stroke or neurological disease (Column 19, lines 1-20 and Column 19, line 63 to Column 20, line 9).

Leptin does not teach the method wherein the reference cell is part of an embryo.

Der et al teaches the method wherein the reference cell is part of an embryo (Column 20, lines 20-40).

Leptin does not teach the method wherein the reference cell is obtained from a mammal neural or neuroblastoma cell.

Der et al teaches the method wherein the reference cell is obtained from a mammal neural or neuroblastoma cell. (Column 19, lines 1-20).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to substitute and combine the method wherein the reference cell is obtained from a mammal neural or neuroblastoma cell or embryo of Der et al. in the method for producing and identifying an active double stranded RNA (dsRNA) which attenuates a desired gene expression in a cell of Leptin since Der et al. states, "The activity of the substances, antibodies, antisense nucleic acid molecules, and composition of the invention may be confirmed in animal experimental model systems. For example, models of peripheral nervous system damage include animals having damaged axons, such as axotomized facial neurons, models of neurodegenerative conditions include the MPTP model, and models of traumatic and non-traumatic peripheral nerve damage include animal stroke (Column 19, line 63 to column 20, line 9)". An ordinary practitioner would have been motivated to substitute and combine the method wherein the reference cell is obtained from a mammal neural or neuroblastoma cell or embryo of Der et al. in the method for producing and identifying an active double stranded RNA (dsRNA) which attenuates a desired gene expression in a cell of Leptin in order to achieve the express advantages, as noted by Der et al., of animal experimental model systems in which the activity of

the substances, antibodies, antisense nucleic acid molecules, and composition of the invention may be confirmed.

Leptin in view of Der et al. do not teach a method, wherein the candidate dsRNA is between 100 and 1100 nucleotides in length.

However, it is *prima facie* obvious that selection of the particular nucleotides number in a candidate gene represents routine optimization with regard to the quality as well as the quantity of the total number of nucleotide content of the candidate gene to be studied which routine optimization parameters are explicitly recognized to an ordinary practitioner in the relevant art. As noted *In re Aller*, 105 USPQ 233 at 235,

> More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the particular nucleotides number selection performed was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art.

4. Claims 19-20 are rejected under 35 U.S.C. 103(a) over Leptin (U.S. Patent 6,135,942) (October 24, 2000) in view of Der et al (U.S. Patent 6,077,686) (June 20, 2000) further in view of Petryshyn (U.S. Patent 6,124,091) (September 26, 2001).

Leptin in view of Der et al. teach a method of claims 14-15, 17, 23-25, 30, 31, 34-36, 43, and 52-53 as described above.

Leptin in view of Der et al. do not teach a method, wherein the step of producing a plurality of cDNA further comprises producing cDNAs of a similar length by digesting cDNA of step (ii) with a restriction enzyme.

Petryshyn teaches a method, wherein the step of producing a plurality of cDNA further comprises producing cDNAs of a similar length by digesting cDNA of step (ii) with a restriction enzyme (Figure 2A and Example 1).

Leptin in view of Der et al. do not teach a method, wherein the step (b) of producing the candidate dsRNA comprises:

(I) producing a plasmid or PCR fragment from the cDNA, and

(Ii) producing the candidate dsRNA from the plasmid or PCR fragment.

Petryshyn teaches a method, wherein the step (b) of producing the candidate dsRNA comprises:

(I) producing a plasmid or PCR fragment from the cDNA (Example 1), and

(Ii) producing the candidate dsRNA from the plasmid or PCR fragment (Examples 1 and 4)

Leptin in view of Der et al. do not teach a method not teach a method, wherein the plurality of cDNA comprises at least a portion of substantially all genes that are actively expressed in the cell.

Petryshyn teaches a method, wherein the plurality of cDNA comprises at least a portion of substantially all genes that are actively expressed in the cell (Example 1)

Leptin does not teach a method, wherein the desired effect of the candidate dsRNA on the reference cell is a result of the candidate dsRNA attenuating expression of a candidate gene in the reference cell.

Petryshyn teaches a method, wherein the desired effect of the candidate dsRNA on the reference cell is a result of the candidate dsRNA attenuating expression of a candidate gene in the reference cell (Example 1).

Leptin in view of Der et al. do not teach a method, wherein the candidate dsRNA has complete sequence identity with the candidate gene over at least 500 nucleotides and in between 500 and 1100 nucleotides in length.

Petryshyn teaches a method, wherein the candidate dsRNA has complete sequence identity with the candidate gene over at least 500 nucleotides and in between 500 and 1100 nucleotides in length (Column 3, lines 7-10).

Leptin in view of Der et al. do not teach a method wherein the reference cell is part of a cell culture.

Petryshyn teaches a method wherein the reference cell is part of a cell culture (Abstract).

It would have been *prima facie* obvious to one having ordinary skill in the art

at the time the invention was made to substitute and combine the method wherein the step of producing a plurality of cDNA further comprises producing cDNAs of a similar length by digesting cDNA of step (ii) with a restriction enzyme.

wherein the step (b) of producing the candidate dsRNA comprises:

(I) producing a plasmid or PCR fragment from the cDNA, and

(Ii) producing the candidate dsRNA from the plasmid or PCR fragment. of Petryshyn in the method for producing and identifying an active double stranded RNA (dsRNA) which attenuates a desired gene expression in a cell of Leptin in view of Der et al. since Petryshyn states, "A method of inhibiting cell proliferation in bone marrow cells obtained from a patient suffering from a hematological cancer is also provided by the present invention ( Column 5, lines 34-36)". An ordinary practitioner would have been motivated to substitute and combine the method wherein the step of producing a plurality of cDNA further comprises producing cDNAs of a similar length by digesting cDNA of step (ii) with a restriction enzyme ( ).

wherein the step (b) of producing the candidate dsRNA comprises:

(I) producing a plasmid or PCR fragment from the cDNA, and

(Ii) producing the candidate dsRNA from the plasmid or PCR fragment. of Petryshyn in the method for producing and identifying an active double stranded RNA (dsRNA) which attenuates a desired gene expression in a cell of Leptin in view of Der et al. in order to achieve the express advantages, as noted by Petryshyn, of an invention which provides a method of

inhibiting cell proliferation in bone marrow cells obtained from a patient suffering from a hematological cancer.

5. Claim 22 is rejected under 35 U.S.C. 103(a) over Leptin (U.S. Patent 6,135,942) (October 24, 2000) in view of Der et al (U.S. Patent 6,077,686) (June 20, 2000) further in view of Petryshyn (U.S. Patent 6,124,091) (September 26, 2001). further in view of kreitman et al. (U.S. Patent 6,027,876) (February 22, 2000).

Leptin in view of Der et al further in view of Petryshyn teach a method of claims 19-20 as described above.

Leptin in view of Der et al. further in view of Petryshyn do not teach a method, wherein the restriction enzyme is Rsa1.

kreitman et al. teach the method wherein the restriction enzyme is Rsa1 (Figure 2 and Column 7, lines 16-22).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to substitute and combine the method wherein the restriction enzyme is Rsa of kreitman et al. in the method for producing and identifying an active double stranded RNA (dsRNA) which attenuates a desired gene expression in a cell of Leptin in view of Der et al. further in view of Petryshyn since kreitman et al. states, "Any restriction enzyme which produces a detectable polymorphism can be used. Preferably, the enzyme used will be a 4-cutter, such as Sau96I, RsaI (Column 7, lines 18-21)". An ordinary practitioner would have been motivated to substitute and combine the method wherein the restriction enzyme is Rsa of kreitman

et al. in the method for producing and identifying an active double stranded RNA (dsRNA) which attenuates a desired gene expression in a cell of Leptin in view of Der et al. further in view of Petryshyn in order to achieve the express advantages, as noted by kreitman et al., of a restriction enzyme which produces a detectable polymorphism which is preferably a 4-cutter, such as Sau96I, RsaI.

8. Claims 27 and 29 are rejected under 35 U.S.C. 103(a) over Leptin (U.S. Patent 6,135,942) (October 24, 2000) in view of Der et al (U.S. Patent 6,077,686) (June 20, 2000) further in view of Villeponteau et al. (U.S. Patent 6,300,110 B1) (October 9, 2001).

Leptin in view of Der et al teach a method of claims 14-15, 17, 23-25, 30, 31, 34-36, 43, and 52-53 as described above.

Leptin in view of Der et al. do not teach a method, wherein the step of selecting the candidate gene comprises:

I) preparing

a) a tester-normalized cDNA library which is a normalized library prepared from test cells;

b) a driver-normalized cDNA library which is a normalized library prepared from test cells;

c) a tester-subtracted cDNA library which is enriched in one or more genes that are up-regulated with respect to the test cell and the control cell, and

d) a driver-subtracted cDNA library which is enriched in one or more genes that are down-regulated with respect to the test cell and the control cell, and

ii) identifying one or more clones from the normalized libraries and/or the subtracted libraries,

wherein the candidate gene is one of the clones identified.

Villeponteau et al. teach the method wherein the step of selecting the candidate gene comprises:

I) preparing

a) a tester-normalized cDNA library which is a normalized library prepared from test cells;

b) a driver-normalized cDNA library which is a normalized library prepared from test cells;

c) a tester-subtracted cDNA library which is enriched in one or more genes that are up-regulated with respect to the test cell and the control cell, and

d) a driver-subtracted cDNA library which is enriched in one or more genes that are down-regulated with respect to the test cell and the control cell, and

ii) identifying one or more clones from the normalized libraries and/or the subtracted libraries,

wherein the candidate gene is one of the clones identified.(Column 33, line 19 to column 34, line 42).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to substitute and combine the method wherein the step of selecting the candidate gene comprises:

I) preparing

a) a tester-normalized cDNA library which is a normalized library prepared from test cells;

b) a driver-normalized cDNA library which is a normalized library prepared from test cells;

c) a tester-subtracted cDNA library which is enriched in one or more genes that are up-regulated with respect to the test cell and the control cell, and

d) a driver-subtracted cDNA library which is enriched in one or more genes that are down-regulated with respect to the test cell and the control cell, and

ii) identifying one or more clones from the normalized libraries and/or the subtracted libraries,

wherein the candidate gene is one of the clones identified of Villeponteau et al. in the method for producing and identifying an active double stranded RNA (dsRNA) which attenuates a desired gene expression in a cell of Leptin in view of Der et al. since Villeponteau et al. states, "The resultant recovered product species (typically an expressed sequence tag or EST cDNA) can be subcloned into a replicable vector with or without attachment of linkers, amplified further, and/or sequenced directly. Once the EST is recovered, it can be used to obtain a substantially full length cDNA from a cDNA library (Column 34, lines 43-48)". An ordinary practitioner would have been motivated to substitute and combine the method wherein the step of selecting the candidate gene comprises:

I) preparing

a) a tester-normalized cDNA library which is a normalized library prepared from test cells;

b) a driver-normalized cDNA library which is a normalized library prepared from test cells;

c) a tester-subtracted cDNA library which is enriched in one or more genes that are up-regulated with respect to the test cell and the control cell, and

d) a driver-subtracted cDNA library which is enriched in one or more genes that are down-regulated with respect to the test cell and the control cell, and

ii) identifying one or more clones from the normalized libraries and/or the subtracted libraries,

wherein the candidate gene is one of the clones identified of Villeponteau et al. in the method for producing and identifying an active double stranded RNA (dsRNA) which attenuates a desired gene expression in a cell of Leptin in view of Der et al. in order to achieve the express advantages, as noted by Villeponteau et al, of a method which can be used to obtain a substantially full length cDNA from a cDNA library.

6. Claims 45-47 and 51 are rejected under 35 U.S.C. 103(a) over Leptin (U.S. Patent 6,135,942) (October 24, 2000) in view of Der et al (U.S. Patent 6,077,686) (June 20, 2000) further in view of Staddon et al. (U.S. Patent 6,312,686 B1) (November 6, 2001).

Leptin in view of Der et al teach the method of claims 14-15, 17, 23-25, 30, 31, 34-36, 43, and 52-53 as described above.

Leptin in view of Der et al do not teach the method, wherein the reference cell has increased sensitivity to N-methyl-D-aspartate and the detecting step comprises detecting a decrease in cellular sensitivity to N-methyl-D-aspartate.

Staddon et al. teach the method, wherein the reference cell has increased sensitivity to N-methyl-D-aspartate and the detecting step comprises detecting a decrease in cellular sensitivity to N-methyl-D-aspartate (Column 14, lines 7-67).

Leptin in view of Der et al do not teach the method, wherein the detecting step comprises detecting modulation of ligand binding to a protein by determining whether the protein encoded by the candidate gene binds to another protein to form a complex that is coimmunoprecipitated.

Staddon et al. teach the method, wherein the detecting step comprises detecting modulation of ligand binding to a protein by determining whether the protein encoded by the candidate gene binds to another protein to form a complex that is coimmunoprecipitated (Figures 12-16 and Column 17, lines 5-37).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to substitute and combine the method wherein the detecting step comprises detecting modulation of ligand binding to a protein by determining whether the protein encoded by the candidate gene binds to another protein to form a complex that can be coimmunoprecipitated of Staddon et al. in the method for producing and identifying an active double stranded RNA (dsRNA) which attenuates a desired gene expression in a cell of Leptin in view of Der et al since Staddon et al. states, "The invention therefore has use in a method of reducing permeability of a physiological barrier such as the blood-brain barrier, the method comprising administering to a subject an effective amount of an agent which promotes tyrosine protein dephosphorylation (Column 3, lines 20-24)". An ordinary practitioner would have been

motivated to substitute and combine the method wherein the detecting step comprises detecting modulation of ligand binding to a protein by determining whether the protein encoded by the candidate gene binds to another protein to form a complex that can be coimmunoprecipitated of Staddon et al. in the method for producing and identifying an active double stranded RNA (dsRNA) which attenuates a desired gene expression in a cell of Leptin in view of Der et al in order to achieve the express advantages, as noted by Staddon et al., of an invention which has use in a method of reducing permeability of a physiological barrier such as the blood-brain barrier, the method comprising administering to a subject an effective amount of an agent which promotes tyrosine protein dephosphorylation.

7. Claims 54-55 are rejected under 35 U.S.C. 103(a) over Leptin (U.S. Patent 6,135,942) (October 24, 2000) in view of Der et al (U.S. Patent 6,077,686) (June 20, 2000) further in view of Panetta et al. (U.S. Patent 6,251,928 B1) (June 26, 2001).

Leptin in view of Der et al teach the method of claims 14-15, 17, 23-25, 30, 31, 34-36, 43, and 52-53 as described above.

Leptin in view of Der et al do not teach the method, wherein the mammalian neural cell of interest or reference cell is a glial cell.

Panetta et al. teach the method, wherein the mammalian neural cell of interest or reference cell is a glial cell (Column 40, lines 30-35).

It would have been *prima facie* obvious to one having ordinary skill in the art

at the time the invention was made to substitute and combine the method, wherein the mammalian neural cell of interest or reference cell is a glial cell of Panetta et al. et al. in the method for producing and identifying an active double stranded RNA (dsRNA) which attenuates a desired gene expression in a cell of Leptin in view of Der et al. since Pinetta et al. states, "Because of the debilitating effects of Alzheimer's disease there continues to exist a need for effective treatments. This invention provides methods for the treatment of Alzheimer's disease in mammals (Column 2, lines 29-32)". An ordinary practitioner would have been motivated to substitute and combine the method, wherein the mammalian neural cell of interest or reference cell is a glial cell of Panetta et al. et al. in the method for producing and identifying an active double stranded RNA (dsRNA) which attenuates a desired gene expression in a cell of Leptin in view of Der et al. in order to achieve the express advantages, as noted by Panetta et al., of an invention which provides methods for the effective treatment of Alzheimer's disease in mammals.

***Response to Amendment***

8. In response to amendment, 112(second paragraph) and 102 rejections are hereby withdrawn. However, new 103(a) rejections have been included.

***Response to Arguments***

9. Applicant's arguments with respect to withdrawal of 112(second paragraph) and 102 rejections have been considered but are moot in view of the withdrawal and new ground(s) of rejection.

Applicant's arguments filed on March 19, 2003 to withdraw 103(a) rejections have been fully considered but they are not persuasive.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Applicant argues that there is no motivation to combine the references. This argument is not persuasive, especially in the presence of strong motivation provided by Der et al since Der et al states, "The activity of the substances, antibodies, antisense nucleic acid molecules, and composition of the invention may be confirmed in animal experimental model systems. For example, models of peripheral nervous system damage include animals having damaged axons, such as axotomized facial neurons, models of neurodegenerative conditions include the MPTP model, and models of traumatic and non-traumatic peripheral nerve damage include animal stroke (Column 19, line 63 to column 20, line 9)". This logic is applicable to other references as well.

Applicant then argues the 103 rejections are improper because it lacks a reasonable expectation of success.

With regard to the "obvious to try" argument, The MPEP 2143.02 states "Obviousness does not require absolute predictability, however, at least some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness. In re Rinehart , 531 F.2d 1048, 189 USPQ 143 (CCPA

1976) (Claims directed to a method for the commercial scale production of polyesters in the presence of a solvent at superatmospheric pressure were rejected as obvious over a reference which taught the claimed method at atmospheric pressure in view of a reference which taught the claimed process except for the presence of a solvent. The court reversed, finding there was no reasonable expectation that a process combining the prior art steps could be successfully scaled up in view of unchallenged evidence showing that the prior art processes individually could not be commercially scaled up successfully.). See also Amgen, Inc. v. Chugai Pharmaceutical Co ., 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir.), cert. denied , 502 U.S. 856 (1991) (In the context of a biotechnology case, testimony supported the conclusion that the references did not show that there was a reasonable expectation of success. 18 USPQ2d at 1022, 1023.); In re O'Farrell , 853 F.2d 894, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988) (The court held the claimed method would have been obvious over the prior art relied upon because one reference contained a detailed enabling methodology, a suggestion to modify the prior art to produce the claimed invention, and evidence suggesting the modification would be successful.)."

There is no evidence of record submitted by applicant demonstrating the absence of a reasonable expectation of success. There is evidence in the Leptin reference of the enabling methodology, the suggestion to modify the prior art, and evidence that a number of different active dsRNAs which attenuate a desired gene expression in a cell (Example and Claims 8-9 and Column 46, line 6 to Column 47, line 46 ), were actually experimentally studied and found to be functional (Column 43, line 13 to Column 44, line 34). This evidence of functionality trumps the

attorney arguments, which argues that Leptin reference is an invitation to research, since Leptin steps beyond research and shows the functional product.

In view of the response to argument, all 103(a) rejections are hereby properly maintained.

***Conclusion***

10. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Arun Chakrabarti, Ph.D. whose telephone number is (703) 306-5818.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (703) 308-1119. Any inquiry of a general nature or

relating to the status of this application should be directed to the Group analyst Chantae Dessau whose telephone number is (703) 605-1237. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission via the P.T.O. Fax Center located In Crystal Mall 1. The CM1 Fax Center numbers for Technology Center 1600 are either (703) 746-4979. Please note that the faxing of such papers must conform with the Notice to Comply published In the Official Gazette, 1096 OG 30 (November 15, 1989).

Arun Chakrabarti

Patent Examiner

Art Unit 1634

April 10, 2003

GARY BENZION, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600